DATE: January 29, 1999; revised 2/3/99

FROM: Daniel Kearns, HFM-675

TO: BLA reference number 98-0261

THROUGH: Julia Gorman, Branch Chief, HFM-675

SUBJECT: Serono BLA 98-0261, CMC section

This is a Biologics License Application for Rebif® (interferon beta-1a). The indication is for relapsing-remitting multiple sclerosis XXXXXXXXXX. The bulk product is manufactured using recombinant DNA using Chinese Hamster Ovary cells at XXXXXXXXXX. The final product is formulated and filled into syringes at XXXXXXXXXX. Packaging also occurs at XXXXXXXXXX.

The submission was reviewed using the Guidance for Industry for the Submission of Chemistry, Manufacturing, and Controls Information for a Therapeutic Recombinant DNA-Derived Product or Monoclonal Antibody Product for In Vivo Use.

There are three drug master files referenced (see volume 1) for the syringe, stopper formulation, and for the XXXXXXXXXX facility.

The description of the drug substance is contained in volume 1.3 and contains more than 23 analytical methods for characterization of the product. Information on the lots used for these characterizations was also provided.

The names, addresses, and registration numbers of the facilities involved in the manufacture of this product are in volume 1.3, page 96. Rebif® has been approved in nine countries, and according to the submission (volume 1.2, page 118) has never been withdrawn or suspended from marketing in any country for safety or effectiveness reasons.

The XXXXXXXXXX location was inspected from November 9 through 13, 1998. There were two minor observations as a result of this inspection. The site has been inspected by FDA 6 times previously, as a number of contract pharmaceutical operations are performed by XXXXXXXXXX for other pharmaceutical manufacturers. As detailed in the EIR, XXXXXXXXXX has never received adverse regulatory actions by FDA. Also noted during the inspection was that the clean bench used for compounding was

dedicated to Rebif® and that in addition (according to batch record instructions), the room can only have Rebif® being compounded. The BLA states (volume 1.5, page 006) that different products could be handled on different clean benches.

Organizational charts were submitted in volume 1.3, page 97. Operations at XXXXXXXXXX are multiproduct, with XXXXXXXXXX used for segregation and contamination prevention. Fillings are performed with dedicated product contact equipment.
Floor diagrams are contained in volume 1.3, page 112.
Contamination precautions are also in volume 1.3, and begin on page 132.

A listing of raw materials and reagents are in volume 1.3, page 143. Flow charts begin on page 162. The cell seed lot system is described beginning on page 309.

The cell line was characterized according to the “Points to Consider in the Characterization of Cell Lines Used for production of Biologicals” (volume 1.2, page 125).

A flow diagram of the bulk production process and in-process controls is in volume 1.2, pages 129 to 134. Specifications and analytical methods are delineated on page 134.

Volume 1.3 contains, in addition to characterization of the drug substance, descriptions (including floor diagrams) of the purified and WFI water systems, steam, compressed gases, HVAC, and electric power supply. There is also contamination precaution descriptions. There is also a list of all components and reagents. The cell seed lot system is described, as well as the facility and bioreactors. Column preparation, validation, storage, and sanitization are described.

Volume 1.4 contains in process controls, including sterility and mycoplasma. Process validation is included, with studies for the cell growth and harvesting process, as well as XXXXXXXXXX operating parameters and batch comparison data. Reference standards are in this section, and also specification and analytical methods. There is a listing of all drug substance specifications and tests used for release testing, shelf life and distribution. Column performance characteristics are described, as well as the viral clearance validation. Impurity testing, including analytical methods and specifications throughout the production process are detailed. Container closure descriptions and routine tests are described. Shipping validation and drug substance stability is included here. Data

for at least three batches or portions thereof are included for all of the above controls, specifications, or tests. All the data reviewed appears to meet the predetermined limits.

Volume 1.5 contains a listing of contract locations, which includes XXXXXXXXXX and a laboratory in Italy for a bioidentity test. Flow charts of the production process are included in this volume for XXXXXXXXXX. Drug product stability data is also contained here. There are various techniques to determine amino acid sequence and structure and the results of such analyzes. The environmental assessment is in this section. Rebif® meets the definition of a naturally occurring substance, and would be entitled to a categorical exclusion from the requirements of filing an environmental assessment under 21 CFR 25.31(c) (exemption for naturally occurring substance).

In addition, the validation of assays used for bulk release testing is in this volume.

Volume 1.6 contains some further physical characterization (XXXXXXXXXX structural analysis). It also contains raw materials and reagents, acceptance criteria for raw materials, and certificate of analyzes, as well as curriculum vitae of key personnel.

Volume 1.7 contains various sequencing reports for both XXXXXXXXXX and XXXXXXXXXX clones used in the manufacture of Rebif®.

Volume 1.8 contains the validation of the master and working cell banks for freedom from adventitious agents.

It was my intention to comment on the inspection findings of the XXXXXXXXXX site in this review. However, there have been two contingencies that have delayed the inspection to the XXXXXXXXXX site. XXXXXXXXXX. The inspection is now scheduled for February 7 through February 11, 1999.

I find that the guidance with regard to the CMC section has been followed by Serono, with information submitted that addresses all aspects of the manufacture of Rebif®. I found for the data that I reviewed that Serono met their analytical specifications and equipment operating parameters. More evaluation of the controls and manufacturing processes will occur during the upcoming inspection at XXXXXXXXXX. Therefore, I have no questions to ask the manufacturer with regard to the CMC section of this application.